

**AD-A273 492****DOCUMENTATION PAGE**Form Approved  
OMB No. 0704-0188

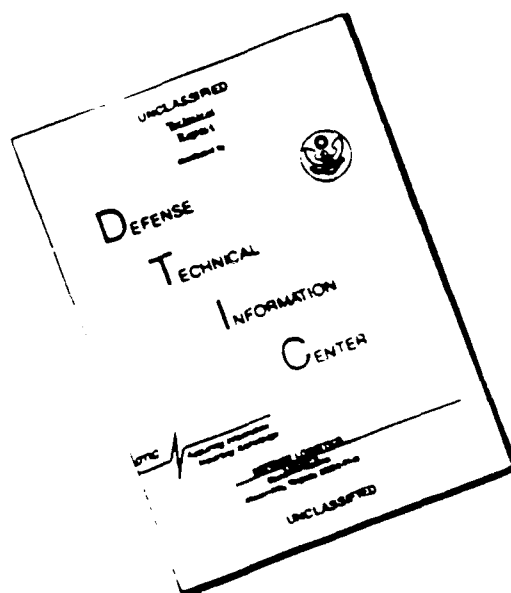
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<b>2. REPORT DATE</b> 1993		<b>3. REPORT TYPE AND DATES COVERED</b> Journal article	
<b>4. TITLE AND SUBTITLE</b> Tyrosine ameliorates a cold-induced delayed matching-to-sample performance decrement in rats		<b>5. FUNDING NUMBERS</b>  PE -61153N PR -MR04120 TA -00D WU -1383	
<b>6. AUTHOR(S)</b> Shurtleff D, Thomas JR, Ahlers ST, Schrot J			
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> Naval Medical Research Institute Commanding Officer 8901 Wisconsin Avenue Bethesda, Maryland 20889-5607		<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>  NMRI 93-60	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> Naval Medical Research and Development Command National Naval Medical Center Building 1, Tower 12 8901 Wisconsin Avenue Bethesda, Maryland 20889-5606		<b>10. SPONSORING / MONITORING AGENCY REPORT NUMBER</b>  DN242603	
<b>11. SUPPLEMENTARY NOTES</b> Reprinted from: Psychopharmacology 1993 vol.112 pp.228-232			
<b>12a. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for public release; distribution is unlimited.		<b>12b. DISTRIBUTION CODE</b>	
<b>13. ABSTRACT (Maximum 200 words)</b>  <div style="text-align: center;"><b>DTIC</b> <b>ELECTE</b> <b>DEC 07 1993</b> <b>S B D</b></div>			
<b>14. SUBJECT TERMS</b> Cold stress, tyrosine, working memory, catecholamines, rats		<b>15. NUMBER OF PAGES</b> 5	
		<b>16. PRICE CODE</b>	
<b>17. SECURITY CLASSIFICATION OF REPORT</b> Unclassified	<b>18. SECURITY CLASSIFICATION OF THIS PAGE</b> Unclassified	<b>19. SECURITY CLASSIFICATION OF ABSTRACT</b> Unclassified	<b>20. LIMITATION OF ABSTRACT</b> Unlimited

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## Tyrosine ameliorates a cold-induced delayed matching-to-sample performance decrement in rats

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Received May 4, 1992 / Final version February 9, 1993

**Abstract.** Exposure to cold stress has been shown to impair short-term, or working, memory which may be related to a reduction in brain catecholamines. Administration of the catecholamine precursor tyrosine may alleviate a cold-stress-induced memory impairment by preventing a deficit in brain catecholamine levels. To test this hypothesis, eight rats performed a delayed matching-to-sample (DMTS) task at an ambient temperature of either 2°C (cold) or 22°C, following intraperitoneal administration of saline or tyrosine (50, 100 or 200 mg/kg). Rats administered saline prior to 22°C exposure demonstrated a characteristic delay gradient in which accuracy decreased as the delay interval between sample and comparison stimuli increased from 1 to 16 s. Consistent with previous research, and relative to 22°C exposure sessions, matching accuracy during 2°C exposure sessions was reduced, which is attributed to the effect of cold on short-term, or working, memory. In particular, during cold exposure sessions matching accuracy was significantly reduced at the longer delay intervals, relative to matching accuracy at 22°C. Additional analysis of cumulative matching errors within sessions showed that during exposure to cold, errors occurred at a constant rate throughout the session, indicating rats' performance was equally debilitated by the stressor over the entire session. During cold exposure sessions, the higher doses of 100 and 200 mg/kg tyrosine significantly improved overall matching accuracy relative to saline, but did not completely reverse the effect of cold exposure, as overall

matching accuracy did not increase entirely to levels obtained at 22°C. A linear slope analysis of cumulative errors within cold sessions indicated that, relative to saline, the higher doses of tyrosine also significantly reduced errors, but did not reduce these errors to levels obtained during exposure to 22°C. It appears that supplemental tyrosine was effective in partially ameliorating the effects of cold stress on DMTS performance, possibly by preventing a cold-stress-induced reduction in brain catecholamine levels.

**Key words:** Cold stress – Tyrosine – Working memory – Catecholamines – Rats

Recent research has shown that exposure to acute cold stress impairs performance on delayed matching-to-sample (DMTS) tasks. This finding has been attributed to the effects of cold on short-term, or working, memory (Thomas et al. 1989, 1991; Ahlers et al. 1991). The deficit in performance on these tasks may be related to cold-stress-induced increases in the release of the central nervous system (CNS) catecholamines, norepinephrine (NE) and dopamine (DA), which results in an overall reduction in neurotransmitter release. The inability of catecholamine neurons to sustain their normal levels of release during exposure to cold could result in an impairment in working memory. A variety of stressors, including cold exposure, have been shown to increase the rate of utilization of NE (Gibson and Wurtman 1978; Brady et al. 1980; Weiss et al. 1980; Palkovits 1984; Reinstein et al. 1984) and DA (Thierry et al. 1976; Brady et al. 1980; Dunn and File 1983; Palkovits 1984; Keefe et al. 1990), which leads to reduction in these CNS catecholamine levels (Gibson and Wurtman 1978; Brady et al. 1980; Weiss et al. 1980; Dunn and File 1983; Palkovits 1984; Reinstein et al. 1984). In addition, reduction in NE and DA CNS levels associated with biochemical lesions has been shown to impair working memory (Brozoskis et al. 1979; Arnsten and Goldman-Rakic 1985). It is also likely

Experiments reported herein were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animal Resources, National Research Council, DHHS Publication (NIH) 86-23, (1985). The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. The research was supported by Naval Medical Research and Development Command research and technology work units 61152N.MR04120.00D.1383 and 62233N.MR03C30.004-1002.

\* This research was conducted while the first author held a National Research Council-NMRI Research Associateship

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that cold-stress-induced reduction in NE and DA release may impair DMTS performance by negatively affecting the release of acetylcholine, a neurotransmitter important in working memory (Decker and McGaugh, 1991).

One important factor necessary for the continued biosynthesis of catecholamines is the availability of the amino acid precursor tyrosine. During acute cold exposure it is possible that the availability of additional tyrosine could result in continuous biosynthesis and sustained release of NE and DA, reducing the working memory deficit. In fact, Gibson and Wurtman (1978) demonstrated that tyrosine can increase the rate at which NE is synthesized in the CNS of rats during acute ambient cold exposure (4°C environment) relative to rats not administered tyrosine and cold stressed. Due to the increased firing rate of CNS neurons and the continued release of catecholamines, tyrosine hydroxylase is activated, leading to an increase in tyrosine utilization and catecholamine biosynthesis (Lovenberg et al. 1978).

In addition to working memory deficits, other cognitive and behavioral deficits have been noted following acute exposure to cold and other stressors, which are believed to be attributed to catecholamine depletion. By possibly allowing for increased catecholamine biosynthesis in neurons, tyrosine has been shown to ameliorate some of these behavioral and cognitive deficits. For example, Banderet and Lieberman (1989) found that human subjects administered tyrosine and then exposed to a simulated high altitude cold stressor (e.g. 4200 m + 15°C) were less debilitated on cognitive tasks, such as addition and pattern recognition, than when performing the tasks without the previous administration of tyrosine. Rauch and Lieberman (1990) also showed that rats administered tyrosine prior to cold water (17°C) immersion stress were less behaviorally depressed than rats exposed to the stressor without the benefit of additional tyrosine.

These data clearly document tyrosine's ability to reduce some of the biochemical, cognitive and behavioral deficits induced by stress. Ultimately, this dietary supplement could become an important factor in preventing, or reducing, a cold-induced memory deficit under field conditions in which exposure to cold-stress is unavoidable. The present experiment, therefore, uses an animal model to determine whether a cold-stress-induced memory deficit can be ameliorated by the administration of tyrosine. The effects of tyrosine on DMTS performance in the absence of cold stress is also reported. In contrast to previous research concerned with the effects of cold stress on working memory (Thomas et al. 1989, 1991; Ahlers et al. 1991), the present experiment examines DMTS errors throughout the entire experimental session. Following changes in error rate over the entire session allows for a more detailed understanding of how cold exposure affects working memory, and how tyrosine impacts on this performance deficit over the session.

## Materials and methods

**Subjects.** Eight Long-Evans rats, maintained at weights of 320–330 g throughout the experiment, were used. The rats had free access to

water, were supplementally fed as needed, and were maintained on a 12 h L/D cycle (lights on at 0600).

**Apparatus.** Two standard operant chambers measuring 20.9 × 21.6 × 29.2 cm were used. The side walls were made of clear Plexiglass, and the front and back walls were made of stainless steel. Two response levers were mounted on the front wall 6.8 cm above the grid floor and 2.5 cm from either of the side walls. A food tray was mounted in the lower center of the front wall, equidistant from each of the levers. The tray was connected by a short tube to a pellet feeder, which delivered 45 mg food pellets. A third response lever was mounted on the opposite wall, 6.8 cm above the grid floor and equidistant from the side walls. A 2.5 cm diameter light with a white lens was mounted 5.7 cm above each of the levers. A houselight was mounted above each operant chamber. All sessions were conducted with the operant chambers housed inside a 61.0 × 71.1 × 121.9 cm temperature-controlled chamber with temperature set at either 22°C or 2°C. Experimental events and data were controlled and recorded by a computer system.

**Procedure.** Rats were placed in an operant chamber 30 min before the start of the session. The session began with the illumination of the houselight and the light above one of the front wall levers (right or left). The rat then had to press the lever under the illuminated light which caused the light to be extinguished, turned on the cue light above the rear wall lever, and initiated a delay interval. A delay interval was randomly selected and could be 1, 2, 4, 8 or 16 s in duration with the following constraint: within a block of 20 trials each delay interval appeared twice, once beginning with the cue light on the left and once beginning with the cue light on the right. No more than four trials with the same delay could occur consecutively. During the delay interval the rat was required to respond on the rear wall lever. The first response on the rear wall lever following completion of the delay interval extinguished the cue light above the rear wall lever, sounded a 2800-Hz tone and illuminated both lights over the front wall levers. A response to the previously responded-to cue lever extinguished both cue lights, was recorded as a correct response, and was followed by the delivery of a food pellet. A response to the previously non-cued lever extinguished both cue lights and was recorded as an incorrect response. A 10-s inter-trial interval preceded the beginning of the next trial. Each session consisted of 180 trials or 75 min, whichever occurred first.

**Tyrosine administration.** L-Tyrosine methyl ester hydrochloride (Aldrich, Milwaukee, WI) was dissolved in 0.9% saline. Saline was used for vehicle control injections. All injections were administered intraperitoneally in a volume of 1.0 ml/kg body wt.

On Tuesdays and Fridays rats were administered either saline or 50, 100, or 200 mg/kg L-tyrosine 15 min prior to being placed in the environmental chamber, which was set at either 2°C (cold exposure) or 22°C for the duration of the experimental session. Each rat experienced all eight combinations of tyrosine or saline administration and temperature exposure in a mixed order. The block of eight conditions was experienced by three of the rats three times and five of the rats twice. The remaining days of the week (M, W, Th) served as baseline days during which the chamber was set at 22°C, and no tyrosine or saline was administered.

**Data analysis.** The mean percent correct for each delay under each condition was computed for each rat. A least squares linear regression analysis was used to characterize the mean rate of change, or slope of cumulative errors over trials, for each condition for each rat. Significant differences between measures (i.e. matching accuracy and slopes of cumulative errors) were assessed using repeated-measures ANOVAs. The least square means multiple comparison test was used to determine differences among paired comparisons. In the case of an insignificant *F*-value, Bonferroni's method (see Milliken and Johnson 1984) was used to assess differences among paired comparisons. Using this method, the obtained  $\alpha$ -value that is used to determine if two conditions are significantly different is  $\alpha/pl$ ; where  $\alpha$  represents the previously used significance level and  $pl$  represents the number of planned comparisons.

## Results

Figure 1 illustrates mean ( $\pm$  SEM) overall matching accuracy during exposure to 2°C and 22°C temperatures for the three doses of tyrosine and the saline condition. Overall matching accuracy significantly changed as a function of temperature and tyrosine dose [ $F(3,21) = 5.70$ ,  $P = 0.0051$ ]. Paired comparisons indicated that cold exposure following saline administration significantly decreased overall matching accuracy relative to the 22°C saline condition ( $P = 0.0001$ ). While matching accuracy did not differ between saline and 50 mg/kg tyrosine at 2°C ( $P = 0.1845$ ), matching accuracy was significantly improved following 100 and 200 mg/kg tyrosine in the cold, relative to saline (both  $PS < 0.002$ ). However, 100 and 200 mg/kg tyrosine did not completely reverse the effects of cold stress, as matching accuracy was significantly lower than following saline administration at 22°C (both  $PS < 0.005$ ). At 22°C, overall matching accuracy following all doses of tyrosine administration was not significantly different from saline (all  $PS > 0.40$ ).

Figure 2 illustrates mean ( $\pm$  SEM) matching accuracy as a function of delay interval during exposure to 2°C and 22°C temperatures for the three doses of tyrosine and the saline condition. There was a significant Temperature by Delay interaction [ $F(4,28) = 6.33$ ,  $P = 0.0009$ ], and paired comparisons indicated that cold exposure, across all doses of tyrosine and saline, significantly reduced matching accuracy at the longer delay intervals of 8 and 16 s relative to 22°C exposure (both  $PS < 0.002$ ). Matching accuracy at the shorter delays was unaffected by cold exposure (all  $PS > 0.07$ ).

Although there was no Temperature by Dose by Delay interaction [ $F(12,84) = 0.77$ ,  $P > 0.68$ ], significant differences among paired comparisons were assessed using Bonferroni's method to compute a new  $\alpha$ -value of 0.0014 (i.e.  $\alpha/pl = 0.05/35$ ). With this significance level, paired comparisons indicated that cold exposure following saline administration significantly reduced matching accuracy at the 4-, 8- and 16-s delays relative to the 22°C saline condition (all  $PS < 0.0014$ ). Relative to the saline cold condition, 200 mg/kg tyrosine dose significantly improved matching in the cold at the 4-s delay ( $P = 0.0001$ ), such that matching accuracy was not different from matching accuracy under the 22°C saline condition ( $P > 0.46$ ). At the 8-s delay, matching accuracy under the 200 mg/kg tyrosine cold condition was marginally, but not significantly, different from the saline cold condition ( $P = 0.009$ ). At the 16-s delay, matching accuracy following 200 mg/kg tyrosine improved in the cold, but not significantly, relative to the saline cold condition ( $P = 0.004$ ). For the 100 mg/kg tyrosine cold condition, matching accuracy tended to improve at the 4- ( $P = 0.0077$ ) and 8-s ( $P = 0.013$ ) delay intervals relative to the saline cold condition, but not significantly under the criteria imposed. For the 50 mg/kg tyrosine dose, matching accuracy was not significantly different from the saline cold condition at any delay interval (all  $PS > 0.14$ ).

Figure 3 illustrates mean cumulative matching errors as a function of trials within a session, for all conditions. Errors in matching occurred at about the same rate

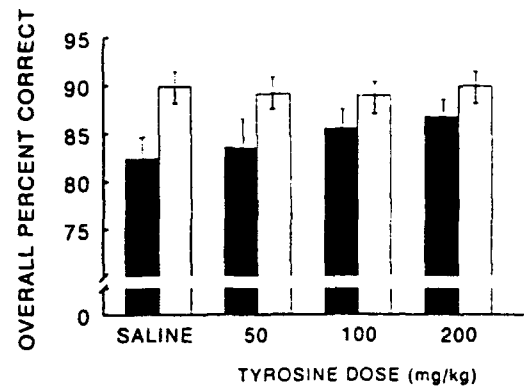


Fig. 1. Mean overall percent correct ( $\pm$  SEM) as a function tyrosine dose and ambient temperature. (■) 2°C; (□) 22°C

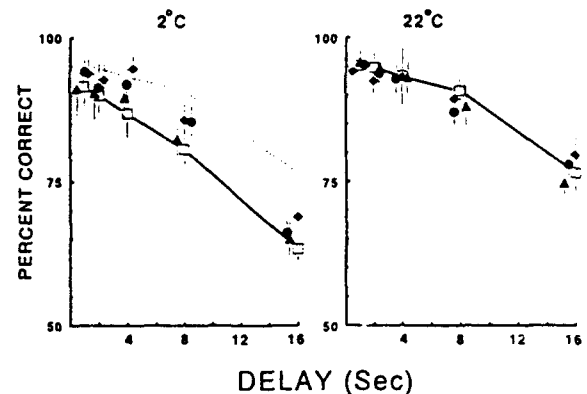


Fig. 2. Mean percent correct ( $\pm$  SEM) matching accuracy as a function of delay interval during exposure to 2°C (left column) and 22°C (right column) air temperatures for three doses of tyrosine, and the saline condition. The dashed line in left column panels represents matching performance during 22°C exposure following saline administration. Some of the data points are positioned to the right or the left of the actual delay interval value for clarity of presentation. (—□—) Saline; (▲) 50 tyr; (●) 100 tyr; (◆) 200 tyr

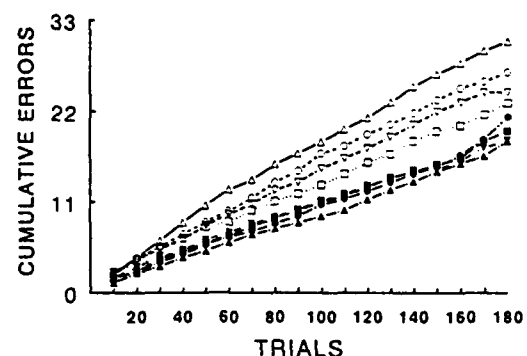


Fig. 3. Mean cumulative matching errors as a function of successive trials within a session for saline and tyrosine conditions during 2°C and 22°C exposures conditions. Temperature 2: (—△—) 0; (—○—) 50; (—▽—) 100; (—□—) 200. Temperature 22: (—▲—) 0; (—●—) 50; (—▼—) 100; (—■—) 200

throughout the session, resulting in a steady increase in cumulative errors. A least squares linear regression analysis adequately described the data for all conditions for all rats (all  $R^2 > 0.95$ ). Analysis of slopes of cumulative

error functions indicated a significant Temperature by Dose interaction [ $F(3,21) = 5.86$ ,  $P = 0.005$ ]. Paired comparisons showed that cold exposure following saline administration significantly increased the slope of cumulative errors relative to the 22°C saline condition ( $P = 0.0001$ ). During cold sessions, the slope characterizing cumulative error rate following 50 mg/kg tyrosine did not significantly differ from saline ( $P > 0.05$ ), while the slopes characterizing cumulative errors for 100 and 200 mg/kg tyrosine were significantly lower, relative to saline (both  $PS = 0.0001$ ). As with overall matching, the slopes of cumulative errors at 2°C following 100 mg/kg and 200 mg/kg tyrosine were significantly greater than the slopes characterizing cumulative errors following saline at 22°C (both  $PS < 0.002$ ) exposure, indicating that tyrosine did not reduce errors in the cold to levels obtained at 22°C. At 22°C, the slopes characterizing cumulative errors following tyrosine administration were not significantly different from the saline condition (all  $PS > 0.20$ ).

## Discussion

Consistent with previous research, acute cold exposure impaired overall matching accuracy (Thomas et al. 1989, 1991; Ahlers et al. 1991), resulting from the longer delay intervals being significantly more affected by cold exposure than shorter delay intervals. Analysis of cumulative errors within a session showed that cold exposure had a constant effect on error rate throughout the session, indicating rats' performance is equally debilitated by the stressor over the entire session. Following an initial half hour of cold exposure, the behavioral data recorded over the remainder of the session indicate that cold stress manifests neither as an acute effect to which the rat adapts within the session, nor as a stressor that gradually impairs performance and increases in apparent intensity over the course of the experimental session.

The higher doses of 100 mg/kg and 200 mg/kg tyrosine significantly improved overall matching accuracy during acute cold exposure. While there was significant improvement in matching accuracy at the 4-s delay following 200 mg/kg tyrosine during cold exposure, in general the beneficial effects of tyrosine on overall matching were not due to improvement at any particular delay interval, but rather due to improvements at several of the delay intervals affected by cold exposure.

Analysis of tyrosine's effects on cumulative errors within cold sessions showed a pattern similar to overall matching accuracy. Higher doses of tyrosine significantly reduced errors at a constant rate throughout the cold sessions, but did not completely reverse the effect of cold, as the error rate was still significantly higher than at 22°C. These data suggest, however, that tyrosine is in sufficient supply in the CNS to benefit DMTS performance throughout the entire cold experimental session.

These results support the hypothesis that cold-stress-induced reduction of CNS catecholamine neurotransmission leads to impaired performance on a DMTS task. Increasing tyrosine availability allows for the repletion of these neurotransmitters, sustaining the release of cate-

cholamines and leading to improved DMTS performance. Furthermore, these data are congruous with previous research attesting to the beneficial effects of tyrosine on a variety of behavioral and cognitive measures during, or following, exposure to other acute stressors (Reinstein et al. 1984; Banderet and Lieberman 1989; Rauch and Lieberman 1990; Ahlers et al. 1992). However, although tyrosine administration ameliorated the effect of cold stress on DMTS performance, it did not completely reverse the effect of cold, and performance levels were not equal to those observed during 22°C exposure.

The behavioral effects associated with tyrosine administration in the absence of exposure to acute stressors have been mixed. Some of the previous research has found no change in spontaneous activity in rats (Mullen et al. 1991), and no change in mood or reaction time in humans (Lieberman et al. 1985) following tyrosine administration. On the other hand, research has demonstrated a reduction in locomotor activity in rats (Reinstein et al. 1984), a reduction in fixed-ratio and fixed-interval responding in rats (Ahlers et al. 1992), increased aggressive behavior in young mice (Brady et al. 1980), and increased open field activity in mice (Gibson et al. 1982) following tyrosine administration. In the present experiment, tyrosine was not behaviorally active in the absence of the thermal stressor. At 22°C, matching accuracy following tyrosine administration was not significantly different from the saline control condition. Since catecholaminergic neurons only utilize tyrosine when they are activated and their firing rate increases, these data suggest that catecholaminergic neurons were unaffected by tyrosine availability due to their relative reduced firing rate, or quiescence, in the absence of thermal stress. However, it is equally possible that increases in catecholamine biosynthesis did occur following supplemental tyrosine administration in the absence of cold stress, but this increase had no effect on performance.

Since central DA and NE levels were not measured in this study, it cannot be determined how these neurotransmitters were affected by cold exposure and tyrosine administration. Previous research, however, has shown that exposure to acute stress reduces NE (Gibson and Wurtman 1978; Brady et al. 1980; Weiss et al. 1980; Palkovits 1984; Reinstein et al. 1984) and DA (Brady et al. 1980; Dunn and File 1983; Palkovits 1984) concentrations in certain regions of the CNS, and tyrosine has been shown to replete the levels of NE in CNS regions implicated in working memory, such as the hippocampus (Reinstein et al. 1984). Furthermore, reduction in either NE or DA in particular brain regions, associated with biochemical lesions, has been related to deficits in working memory (Brozoskis et al. 1979; Arnsten and Goldman-Rakic 1985; Decker and McGaugh 1991). For example, DA and NE terminals in the prefrontal cortex of non-human primates have been implicated in working memory, and research has shown that depleting these catecholamines results in impaired working memory (Brozoskis et al. 1979; Arnsten and Goldman-Rakic 1985). Administration of the NE agonist clonidine has been shown to reduce age-related working memory impairment, improve working memory in animals following NE depletion in the pre-

frontal cortex, and improve working memory in young non-human primates, presumably through the stimulation of post-synaptic, alpha-adrenergic receptors (Arnsten and Goldman-Rakic 1985; Arnsten et al. 1988; Jackson and Buccafusco 1991). Similarly, the DA agonist apomorphine has also been shown to improve working memory following DA depletion in the prefrontal cortex of non-human primates (Brozoskis et al. 1979), while the DA receptor antagonist haloperidol has been shown to impair radial-arm maze performance in rats (Beatty and Rush 1983; Levin 1988). It is clear that both DA and NE are involved in working memory. Further research is needed to determine in what manner cold stress and tyrosine impact on these neurotransmitter systems in the CNS to modulate working memory.

In summary, acute cold stress impaired working memory in rats. The higher doses of 100 and 200 mg/kg tyrosine significantly improved overall matching accuracy and reduced cumulative error rate during exposure to acute cold stress relative to saline, while 50 mg/kg tyrosine did not. Tyrosine had no adverse effects on DMTS performance in the absence of cold stress. It appears that supplemental tyrosine is capable of improving DMTS performance in the cold by preventing a cold-stress-induced reduction in brain catecholamine levels. Taken together with previous research, it is possible that supplemental tyrosine administration could be beneficial in reducing a working memory deficit under field conditions in which exposure to acute cold stress is unavoidable.

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